The withdrawal of the previous objections and/or rejections of claims 1-5 on formal grounds, and also on double patenting, are noted with appreciation.

Reconsideration is requested of the rejection of the present invention under 35 USC 103 as unpatentable, i.e., obvious, over Bani et al, "Relaxin Counteracts Asthma-Like Reaction Induced By Inhaled Antigen In Sensitized Guinea Pigs," Endocrinology 1997, 138/5: 1909-1915 (Bani), in view of Masini et al, Abstract, "Relaxin Inhibits Histamine Release From Mast Cells: Involvement Of Nitric Oxide Production," Inflammation Research 1995, 44 (Suppl. 1): S12-S13 (Masini).

Bani (Abstract) notes that since the peptide hormone relaxin (RLX) was found to inhibit mast cell secretion and platelet activation, and since it has been established that the release of mediators from these cells plays a central pathogenic role in allergic asthma, the authors were prompted to ascertain whether RLX may counteract the respiratory and histopathological abnormalities of the asthma-like reaction to inhaled antigen in sensitized guinea pigs.

Bani (Abstract) found that RLX reduced the severity of respiratory abnormalities, as well as histological alterations, mast cell degranulation, and leukocyte infiltration in sensitized guinea pigs exposed to ovalbumin aerosol, and that RLX also promoted dilation of alveolar blood capillaries and reduced the thickness of the air-blood barrier. Bani indicates that the above provides evidence for an antiasthmatic property of RLX and raises

the possibility of new therapeutic strategies for allergic asthma in humans.

However, Bani (Introduction) considers the above discussed effects to be mediated by a stimulation of the endogenous production of nitric oxide (NO), and on these grounds hypothesizes that RLX may counteract the pathogenic events underlying allergic asthma, further noting that the ability of RLX to stimulate production of nitric oxide by mast cells and platelets strengthens the hypothesis of a beneficial action of RLX in asthma, as nitric oxide has been shown to cause relaxation of lung airways and blood vessels, and hence improve asthmatic symptoms.

In particular, Bani (Discussion) considers many different possible explanations for the action of RLX, including the demonstrated ability of RLX to evoke a response of its targets through stimulation of endogenous production of nitric oxide, which in turn has been shown to exert beneficial effects on asthma by acting on lung components at multiple levels. Bani concludes that the antiasthmatic properties of RLX may also rely on its ability to stimulate nitric oxide production by cells in the lungs.

Indeed, Bani (Discussion, penultimate paragraph) even posits the possibility that the above effects of RLX may explain previous clinical reports of a subjective and objective improvement in asthma during pregnancy.

At best, Bani concerns treatment of allergic asthma-like reaction by a mechanism generally based on endogenous production of

nitric oxide which is itself considered to exert a beneficial effect on asthma.

Bani is not concerned with the instant methods of treating a Th2-dominated disease in a human patient (claims 1, 4 and 5), inhibiting a pathogenic Th2 response in a human patient (claim 2), or stimulating the development of activated human T cells into Th1-like effectors in a human patient (claim 3), let alone the non-elected method of regulating immune homeostasis during pregnancy in a human female patient (claim 6), based on a different mechanism, i.e., stimulation of Th1-like effectors in humans (spec., p. 3, lines 8-19).

As noted herein (spec., p. 2, lines 3-19):

$CD4_+$ Th lymphocytes are classified into different functional subsets based on their profile of cytokine production, e.g. with Th1 cells producing IFN-γ, IL-2 and TNF-β, and Th2 cells producing IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13;

some Th2-derived cytokines, such as IL-4, IL-10 and IL-13, inhibit several macrophage functions;

the development of Th1- or Th2- dominated responses depend on several factors, the most critical being cytokines produced during antigen presentation; and

IFN-γ, IFN-α and IL-12 promote differentiation of naive Th cells into the Th1 pathway, whereas IL-4 appears to be the most dominant factor for determining the Th2 polarization.

According to the present invention, it has been found that RLX has an effect on the differentiation of antigen-specific T cells

into IFN-γ- and/or IL-4- producing cells, and an effect on the production of IFN-γ and IL-4 induced by TCR stimulation of established T cell clones, but with the enhanced ability to produce IFN-γ without exerting any effect on the production of IL-4 (spec., p. 3, lines 8-15; and p. 4, lines 6-10).

Per the instant mechanism, the promoting effect of RLX on the development of IFN-γ- producing cells is not due to RLX-induced release of IT-12 and/or IFN-α by antigen-presenting cells (spec., p. 3, line 24, to p. 4, line 2). Indeed, RLX increases both IFN-γ mRNA expression and IFN-γ production induced by TCR stimulation of established $CD4^+$ T cell clones, suggesting that RLX can directly influence both differentiation and function of $CD4^+$ effector T lymphocytes (spec., p. 4, lines 10-14).

The technical prejudice in Bani, based on a treating mechanism of RLX which involves endogenous production of nitric oxide for treating asthma-like allergic reaction, renders this teaching remote herefrom. Bani does not suggest that RLX may have any effect on the Th2 response as per the present invention.

Masini (Abstract) concerns a mechanism of RLX which inhibits histamine release from isolated rat serosal mast cells, involving nitric oxide production. Masini concludes that RLX-induced vasodilation seems dependent, at least in part, on local production of NO (nitric oxide) by mast cells, raising the possibility that RLX may be used to treat allergic and peripheral vascular diseases.

The technical prejudice in Masini, based on a treating mechanism of RLX which involves endogenous production of nitric

oxide for treating allergic and peripheral vascular diseases, likewise renders this teaching remote from the present invention. Hence, like Bani, Masini does not suggest that RLX may have any effect on the Th2 response as per the present invention.

It is noted that Masini (as of 1995) predates Bani (as of 1997), and thus Bani follows the technical prejudice of Masini as to preoccupation of the mechanism of action of RLX as causing the endogenous production of nitric oxide, which itself has beneficial effects on asthma-like allergic symptoms, as earlier noted.

In contrast thereto, the instant invention is directed to the novel use of RLX as an agent suitable for treating Th2-dominated diseases, based on the recognition that RLX has an inhibiting effect on pathogenic Th2 response.

Bani and Masini collectively relate only to the use of RLX for treating asthma or the like, based on several suggested mechanisms of action to explain the effect of RLX, e.g., on asthma or asthma-like reaction, the main mechanism of action noted in Bani in this regard being the depression of histamine release caused by RLX (Discussion).

Nowhere in Bani or Masini is there any suggestion that RLX may have any effect on the Th2 response. Instead, the recognition that RLX has an effect on the Th1 versus Th2 response, i.e., of the human organism, is attributable only to the present inventor, and this inherent effect of RLX as discovered by the present inventor opens the way to application of RLX for treatment of many diseases beyond asthma.

The mechanism of action per the instant invention is clearly different from any contemplated in Bani and/or Masini. Indeed, while in these two references RLX is used to stimulate NO synthesis and to depress histamine release, per the present invention RLX is used to stimulate an entirely different mechanism, namely to stimulate the Th1-like effectors. This novel inherent effect of RLX could not be foreseen by the skilled artisan from Bani and/or Masini, and therefore the instant methods of using RLX cannot be considered obvious.

Since Bani and Masini provide explanations of the mechanism of action of RLX generally involving production of nitric oxide, there would be no reason to motivate the skilled artisan to modify the Bani and Masini collective teachings that would involve the inherent effect of RLX for inhibiting pathogenic Th2 response.

This motivation could only occur by impermissible hindsight use of the instant invention itself to show that it is not an invention.

In this regard, the Examiner asserts that asthma is inherently a Th2-dominated disease, that Th1 cells inherently secrete IFN-γ and RLX inherently favors development of IFN-γ, and that IFN-γ will have the inherent biological activity of enhancing a Th1 response or stimulating Th1-like effectors.

However, Bani and Masini do not teach that RLX has an inhibiting effect on pathogenic Th2 response, and while the instant mechanism of action may be inherent in the use of RLX per the invention, it is clearly not obvious from the pertinent prior art.

It is impermissible for an Examiner to hold that inherent features and advantages of an invention are relevant to obviousness and somehow demonstrate that the invention is obvious, since inherency of an advantage and its obviousness are entirely different questions. In re Spormann, 150 USPQ 449, 452 (1966); In re Adams, 148 USPQ 742, 745-746.

As stated in the Spormann case, at page 452:

> "The board apparently thought that the minimizing of sulfate production would be inherent in the process of Friedrich et al. However, this is no support for a rejection for various reasons. Friedrich et al. make no mention of it, as the board conceded. Their process is not appellants' process. It is a reaction between solid, powered material and gas, the only water present being chemically combined water and hygroscopic water; appellants react sprayed solution and gas. As we pointed out in In re Adams, 53 CCPA 996, 356 F.2d 998, 148 USPQ 742, the inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." (Emphasis in original.)

Clearly, the present inventor was the first to recognize the novel use of RLX for treating Th2-dominated diseases, based on the recognition per the present invention that RLX has an inhibiting effect on pathogenic Th2 response.

Furthermore, as stated in the Adams case, at pages 745-746:

"The Patent Office presents a number of hindsight arguments. It says Adams was not the first to use foam for heat transfer as fire departments and fire extinguisher users have been squirting foam on fires for years and housewives have been pouring aerated hot water on cold plates in the kitchen sink for years, in both of which operations heat transfer is inherent. Of course it is inherent, otherwise appellant's invention would not work. But patentability here does not hinge on inherency. It depends on the unexpected and unsuggested increase in heat transfer efficiency. No reference suggesting this has been produced, only ex post facto explanations as to why anyone should have been able to see that it would be more efficient to use aerated water....The examiner made no attempt to explain why it would be obvious, other than to say aerating or foaming rinse water is commonplace. The board opined that 'it is axiomatic that heat transfer will be improved by subjecting articles to be cooled to a stream of cooling liquid with minimum waste by splashing and a stream which is so formed that the contact between the articles and the stream particles is increased.' It felt using Aghnides nozzles to reduce splashing and increase contact would be an obvious change in a heat transfer method but we regard this as mere hindsight analysis of appellant's teaching

with no basis at all in the absence of access to his teachings." (Emphasis in original.)

As to inherency, the Adams court further stated, at page 746:

"Finally, the solicitor adds the argument that the superiority of appellant's heat transfer is inherent in the use of the foam. Again we observe that, of course, it is. But the art does not suggest the use of foam in heat transfer of any kind and there is not the slightest suggestion that anyone knew of the existence of this inherent superiority until Adams disclosed it. After all, Bell's telephone was 'inherently' capable of transmitting speech, DeForest's triode was 'inherently' capable of amplification, and, to come down to date, so was the tiny transistor which is rapidly supplanting it. Two of our decisions are cited as supporting the erroneous notion that 'subject matter cannot be patented on the basis of an inherent property.' We think the proposition thus broadly stated and as applied here is so transparently erroneous as not to require discussion." (Emphasis in original.)

Accordingly, the obviousness rejection, tacitly based on inherency of applicant's invention to be within the collective teaching of Bani and Masini, is believed to be unwarranted and should be withdrawn.

In this regard, it is noted that the Examiner has commented on the import of certain of the references [1] to [13] discussed in the Supplemental Amendment dated April 23, 2002, copies of some of which were submitted with the April 1, 2002 Amendment.

[1] Romagnani I (Romagnani, Int J Clin Lab Res 1996, 26:83-98) merely indicates (p. 92, col. 2) that RLX was found to favor development of IFN-γ- and TNF-β- producing cells, without having any influence on IL-4 and IL-5 production, thus showing an opposite effect to progesterone, with increasing evidence suggesting that hormones and peripherally activated prohormones may regulate the Th1/Th2 balance. [1] Romagnani I does not teach the instant concept.

[2] Grunewald (Grunewald et al., J Immunol 1998, 160:4004-4009) relates to the effects of an antagonistic murine IL-4 mutant (QY), and is not concerned with the effects of RLX as contemplated herein.

[3] Romagnani II (Romagnani, Ann Allergy Asthma Immunol 2000, 85:9-21) relates to properties of Th1 versus Th2 cells, and is not concerned with the effects of RLX as contemplated herein.

[4] DeKruyff US-898 (U.S. Patent No. 6,086,898, issued July 11, 2000 to DeKruyff et al.) relates to the use of a combination of an antigen and a specific type Listeria adjuvant for converting a Th2-type allergic immune response to such antigen into a Th1-type response, and is not concerned with the effects of RLX as contemplated herein. Indeed, [4] DeKruyff US-898 would lead the skilled artisan away from the present concept in that it would point Bani

and Masini in the direction of use of a Listeria type bacterium, rather than a hormone such as RLX, for achieving desired responsive effects of Th1-cells versus Th2-cells. [4] DeKruyff US-898 has nothing to do with the present invention.

[5] Levinson US-322 (U.S. Patent No. 6,066,322, issued May 23, 2000 to Levinson) relates to the use of an antibody specific for a 103 gene product to treat a TH2 or TH2-like-mediated asthma condition, and has nothing to do with RLX as contemplated by the present invention.

[6] Levinson US-887 (U.S. Patent No. 6,156,887, issued December 5, 2000 to Levinson) relates to a specific type isolated polypeptide, and has nothing to do with RLX as contemplated by the present invention.

[7] Levinson US-909 (U.S. Patent No. 6,190,909, issued February 20, 2001 to Levinson et al.) relates to an isolated specific nucleic acid molecule, and has nothing to do with RLX as contemplated by the present invention.

[8] Levinson US-218 (U.S. Patent No. 6,288,218, issued September 11, 2001 to Levinson) relates to a method for detecting a specific 200 gene expression, and especially for diagnosing a TH cell subpopulation related immune disorder involving such 200 gene expression. [8] Levinson US-218 has nothing to do with RLX as contemplated by the present invention.

[9] Kingsbury US-334 (U.S. Patent No. 6,323,334, issued November 27, 2001 to Kingsbury et al.) relates to an isolated

specific type nucleic acid molecule, and has nothing to do with RLX as contemplated herein.

[10] Levinson US-351 (U.S. Patent No. 5,721,351, issued February 24, 1998 to Levinson) is a continuation in part (CIP) of [5] Levinson US-322; [11] Levinson US-498 (U.S. Patent No. 6,066,498, issued May 23, 2000 to Levinson) is a division of [10] Levinson US-351 and in turn a CIP of [5] Levinson US-322; [12] Levinson US-083 (U.S. Patent No. 6,084,083, issued July 4, 2000 to Levinson) is a division of [13] Levinson US-371 (U.S. Patent No. 6,204,371, issued March 20, 2001 to Levinson) which is a CIP of [10] Levinson US-351 and in turn of [5] Levinson US-322; and [13] Levinson US-371 is a CIP of [10] Levinson US-351 and in turn of [5] Levinson US-322.

Hence, such patents [10] to [13] are deemed to duplicate generally the content of such patents [5] to [9], so that only the articles [1] to [3] and patents [4] to [9] are discussed above, with patents [10] to [13] being regarded as cumulative thereto.

References [1] to [9] have been discussed in detail in the Supplemental Amendment dated April 23, 2002 (pages 5-17 thereof, the contents of which are incorporated herein by reference), as to their positive import as prior art background for the advance thereover provided by the present invention, e.g., in terms of Th1 versus Th2 effects of various substances, and are discussed hereinabove as to their negative import in regard to the absence of any teaching therein of the effect of RLX on the Th2 response as contemplated by the present invention.

Although various of the above discussed references may by hindsight indicate the inherency of the mechanism of action of RLX as contemplated herein, such references do not teach that RLX possesses such inherent mechanism of action, which mechanism of action has for the first time been recognized by the present inventor, and which mechanism of action, absent the present invention, even though inherent, would not have enriched the art but for the present invention recognition thereof to show the way.

As is clear from the instant disclosure, per the present invention, relaxin (RLX) has an effect on the differentiation of antigen-specific $CD4^+$ T cells into IFN-γ (Th1) and/or IL-4 (Th2) producing cells, and on the production of IFN-γ and IL-4 induced by T cell receptor (TCR) stimulation of established T cell clones, permitting development of antigen-specific $CD4^+$ T cells into T cells showing enhanced ability to produce IFN-γ (Th1) without exerting any effect on production of IL-4 (Th2) (spec., p. 3, lines 8-15; p. 4, lines 6-14; and p. 14, lines 1-4 and 6-12). Such promoting effect of relaxin on development of IFN-γ producing cells is not due to relaxin induced release of IL-12 and/or IFN-α by antigen presenting cells (APC) (spec., p. 3, line 24, to p. 4, line 2; p. 12, lines 1-10; and p. 12, lines 4-6).

In view of the foregoing, the present invention is believed to be patentable over the pertinent prior art. Withdrawal of the obviousness rejection is accordingly urged.

Reconsideration and allowance are respectfully requested.